ADAM17 deletion in thymic epithelial cells alters aire expression without affecting T cell developmental progression.

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Public Summary:
Cellular interactions between thymocytes and thymic stromal cells are critical for normal T cell development. Thymic epithelial cells (TECs) are important stromal niche cells that provide essential growth factors, cytokines, and present self-antigens to developing thymocytes. Here, we examined T cell and thymic epithelial cell development by using a mouse strain in which the ADAM17 gene was specifically deleted in TECs.Normal T cell lineage choice and development through the canonical alphabeta T cell stages was observed. Interestingly, Adam17 deficiency in TECs resulted in reduced expression of the transcription factor Aire. However, no alterations in the patterns of TEC phenotypic marker expression and thymus morphology were noted. In contrast to expectation, our data clearly shows that absence of Adam17 in TECs is dispensable for normal T cell development. Differentiation of TECs is also unaffected by loss of Adam17 based on phenotypic markers. Surprisingly, we have uncovered a novel genetic link between Adam17and Aire expression in vivo. The cell type in which ADAM17 mediates its non-cell autonomous impact and the mechanisms by which it regulates intrathymic T cell development remain to be identified.

Scientific Abstract:
BACKGROUND: Cellular interactions between thymocytes and thymic stromal cells are critical for normal T cell development. Thymic epithelial cells (TECs) are important stromal niche cells that provide essential growth factors, cytokines, and present self-antigens to developing thymocytes. The identification of genes that mediate cellular crosstalk in the thymus is ongoing. One candidate gene, Adam17, encodes a metalloprotease that functions by cleaving the ectodomain of several transmembrane proteins and regulates various developmental processes. In conventional Adam17 knockout mice, a non-cell autonomous role for ADAM17 in adult T cell development was reported, which strongly suggested that expression of ADAM17 in TECs was required for normal T cell development. However, knockdown of Adam17 results in multisystem developmental defects and perinatal lethality, which has made study of the role of Adam17 in specific cell types difficult. Here, we examined T cell and thymic epithelial cell development using a conditional knockout approach. METHODOLOGY/PRINCIPAL FINDINGS: We generated an Adam17 conditional knockout mouse in which floxed Adam17 is deleted specifically in TECs by Cre recombinase under the control of the Foxn1 promoter. Normal T cell lineage choice and development through the canonical alphabeta T cell stages was observed. Interestingly, Adam17 deficiency in TECs resulted in reduced expression of the transcription factor Aire. However, no alterations in the patterns of TEC phenotypic marker expression and thymus morphology were noted. CONCLUSIONS/SIGNIFICANCE: In contrast to expectation, our data clearly shows that absence of Adam17 in TECs is dispensable for normal T cell development. Differentiation of TECs is also unaffected by loss of Adam17 based on phenotypic markers. Surprisingly, we have uncovered a novel genetic link between Adam17and Aire expression in vivo. The cell type in which ADAM17 mediates its non-cell autonomous impact and the mechanisms by which it regulates intrathymic T cell development remain to be identified.